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| 10/574,157  | 03/28/2006  | Herman Augustinus De Kock | TIP0051USPCT        | 7766             |
| 27777   | 7590        | 11/09/2010                |                     |                  |
| PHILIP S. JOHNSON<br>JOHNSON & JOHNSON<br>ONE JOHNSON & JOHNSON PLAZA<br>NEW BRUNSWICK, NJ 08933-7003 |             |                           |                     |                  |
| EXAMINER  |             |                           |                     |                  |
| OTTON, ALICIA L.  |             |                           |                     |                  |
| ART UNIT  |             | PAPER NUMBER              |                     |                  |
| 1626  |             |                           |                     |                  |
| NOTIFICATION DATE   |             | DELIVERY MODE             |                     |                  |
| 11/09/2010  |             | ELECTRONIC                |                     |                  |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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### Office Action Summary

**Application No.**

10/574,157

**Applicant(s)**

DE KOCK ET AL

**Examiner**

Alicia L. Otton

**Art Unit**

1626

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 31 August 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 36 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/CD)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

***Status of Claims***

1. Claim 36 is currently pending in the instant application. Claims 1-35 have been cancelled to date.

***Response to Amendments and Arguments***

2. Applicant's arguments and amendments filed August 2, 2010 have been fully considered and entered into the application. All rejections and objections not explicitly maintained herein are withdrawn. The rejections below constitute the full set being applied to the instant claim.

***Maintained Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

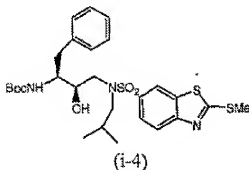
4. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2002/083657 A2 (Surleraux, et al.; publication date October 24, 2002) in view of Patani et al., *Chem Rev.*, 1996, 96, 3147-76, further in view of Chu-Moyer et al., *J. Org. Chem.*, 1995, 60 (17), 5721-5725 and Van der Geest et al. (WO 2003/049746, published June 19, 2003).

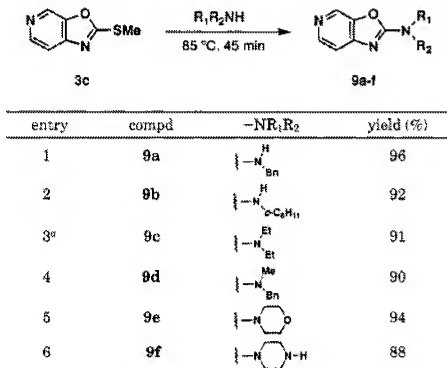
6. The claims are drawn to a method for preparing a compound of formula (9) comprising aminating a compound of formula (6), deprotecting the resulting compound to arrive at a compound of formula (8), and coupling the compound of formula (8) with a radical R1-L to obtain the desired compound.

7. Scheme I on page 43 of the '657 publication discloses compound (i-4), which is a compound of instant formula (6), and also details its synthesis. The compound has the following structure:



8. The above compound corresponds to a compound of instant formula (6) wherein PG is Boc, R2 is H, R3 is phenylmethyl, R4 is isobutyl, E is CH<sub>3</sub>, and the sulfonamide group is attached to the benzoxazole ring at the 6 position. Compound (i-4) is the exact compound as the starting material used in claim 36 (i.e. Compound 6), with the only difference being that the benzothiazole ring in the prior art is a benzoxazole ring in the instant application, which results in the change of the S in the ring to an O.

9. Regarding the process of making compound (9) beginning with compound (6), the '657 publication does not teach the amination of a compound of formula (6) as required by the first step in claim 21. Rather, in the '657 publication compound (i-4) which corresponds to instant formula (6) is oxidized prior to amination, and compounds (i-6) and (i-5) are aminated. However, the amination of an S-alkyl group such as S-Me is a well known nucleophilic aromatic substitution reaction. Chu-Moyer et al. teach the following compounds and reactions:



10. One of ordinary skill in the art would have been motivated at the time the invention was made to alter the steps of the synthesis method by directly aminating the S-Me group rather than oxidizing it first, as is taught in Scheme I. The motivation to do so is based on the fact that the reaction shown about by Chu-Moyer et al. is a well-known synthesis method, which would allow for the elimination of an extra step in the method (namely the oxidation step). The '657 publication teaches that the amination step was carried out over a period of 20 hours and gave a 93% yield (page 44, lines 11 and 14), while the reaction taught by Chu-Moyer et al. was carried out for only 45 minutes, with no significant difference in yield of aminated product, as shown by the table above. The amination step in the '657 publication yields a product which corresponds to instant formula (7) wherein R<sub>8</sub> is hydrogen and R<sub>6</sub> is ethylpyrrolidine (aminoC<sub>1-6</sub>alkyl). Please note that because no definition of the term "amino" was given in the instant specification,

the cyclic amino group (i.e. pyrrolidine) taught by the '657 publication is interpreted as reading on the broader term "amino" as claimed in the definition of R6 and R8.

11. Following the amination step, the '657 patent teaches the deprotection of compound (i-7) on page 44, lines 17-23, which forms a compound that corresponds with instant compound 8. Finally, compound (i-7) was reacted with 1-[[[(3S,3aR,6aS)+(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl]oxy]-2,5-pyrrolidinedione, which had the effect of coupling a radical of instant formula R<sub>1</sub>-L [where L is O-C(=O) and R<sub>1</sub> is a bicyclic heterocycle having 8 ring members] to compound (i-7) to form compound 20. Compound 20 of the '657 publication corresponds to a compound of instant formula (9).

12. To those skilled in the chemical art, compounds are not patentably distinct when the claimed compounds and prior art compounds have a difference of one chalcogen vs. another chalcogen. Since both O and S are chalcogens, the claimed compounds are analogues or isologues of those in the '657 publication. *Ex parte Wiseman*, 98 USPQ 277 (1953). Additionally, the instantly claimed compounds and that of the prior art are bioisosteres of one another. Patani et al. teaches that "bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents," and further that the concept of bioisosterism is "intuitive" (page 3147, Introduction, column 1-column 2). Bioisosteric substitutions are well-known in the art. For example, O and S are isosteric (See Table 25, page 3158, compounds 52a and 52d). Case law has determined that when chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made. See for example *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977) (adjacent homologues and structural isomers); *In re May*, 574 F.2d 1082, 197

USPQ 601 (CCPA 1978) (stereoisomers); In re *Hoch*, 428 F.2d 1341, 166 USPQ 406 (CCPA 1970) (acid and ethyl ester). When such “close” structural similarity to prior art compounds is shown, in accordance with these precedents the burden of coming forward shifts to the applicant, and evidence affirmatively supporting unobviousness is required. Further, as evidenced by Van der Geest et al., which discloses various structurally similar compounds as HIV protease inhibitors, it was known in the art at the time of the invention that for this particular application, benzoxazole and benzothiazole rings were chemical equivalents, expected to have the same utility and function [See, e.g., Table A, p. 43, left column, last compound (amino substituted benzoxazole) vs. p. 43, left column, third from last compound (amino substituted benzothiazole)]. Therefore the state of the art at the time of the invention was that these two ring structures were interchangeable for the purposes of the invention.

13. The instantly claimed compounds would have been *prima facie* obvious to one skilled in the art at the time the invention was made because one skilled in the art would have been motivated to prepare analogues or bioisosteres of the compounds taught by the ‘657 publication with the expectation of obtaining compounds with similar properties and utilities (namely intermediates used to produce pharmacologically active HIV protease inhibitors). Because the compounds would be *prima facie* obvious, as determined above, the methods of making as in claim 36 would have also been *prima facie* obvious, as the steps and the structures of the intermediates used to make compound (9) are all exactly the same as the prior art, with the only difference being the substitution of the sulfur in the prior art for an oxygen in the instant claims in the starting material. However, this difference was known in the art at the time of the invention to be a chemical equivalent and the two ring systems are viewed as being



interchangeable. Regarding the steps involved in starting with compound (6) to produce a compound of formula (9), it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to combine the compounds and method taught by the '657 with the information on bioisosteres from Patani et al. and Van der Geest et al. to obtain compounds with similar activity, and to further combine this with the teachings on amination in Chu-Moyer et al. Chu-Moyer et al. shows that directly aminating an S-Me group is a known reaction which would allow for the synthesis of an aminated ring structure in less time than the method taught by the '657 publication while still obtaining a high yield of aminated product. This it would have been *prima facie* obvious to combine these references with a reasonable expectation of success in producing high yields of HIV protease inhibitor compounds of formula (9).

#### ***Response to Arguments***

14. Applicants traverse the rejection stating that although the rejection is "superficially" correct, without the teaching of applicant's invention there would have been no motivation to try to make the claimed compounds. This is not found persuasive since compounds are not considered to be patentably distinct when the claimed compounds and prior art compounds have a difference of one chalcogen vs. another chalcogen. *Ex parte Wiseman*, 98 USPQ 277 (1953). Further motivation is provided in the Patani reference which teaches the concept of bioisosterism being "intuitive" to medicinal chemists, who are considered to be people of ordinary skill in the art for the present invention. The reference teaches that it is very common for medicinal chemists to modify known compounds in rational ways (such as substitution of one chalcogen

for another, i.e. O vs. S) in order to obtain compounds with similar utilities. Further, case law has determined that when chemical compounds have “very close” structural similarities and similar utilities, without more a *prima facie* case may be made. See for example *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977) (adjacent homologues and structural isomers); *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers); *In re Hoch*, 428 F.2d 1341, 166 USPQ 406 (CCPA 1970) (acid and ethyl ester). When such “close” structural similarity to prior art compounds is shown, in accordance with these precedents the burden of coming forward shifts to the applicant, and evidence affirmatively supporting unobviousness is required.

15. Applicants also argue that the examiner has made “particular and selective choices to combine fragments of the prior art.” This is not found persuasive since only one synthetic scheme (i.e. Scheme I) was used to make the *prima facie* case of obviousness. The reference teaches this scheme as being able to successfully produce the prior art compounds and the selection of a successful synthetic scheme would have provided sufficient motivation for a person of ordinary skill in the art to select and modify the scheme taught in the prior art for the successful synthesis of the known compounds.

16. Applicants finally argue that the complexity of the rejection argues that the combination of references is not straightforward. However, complexity is not viewed as being objective evidence of non-obviousness. Further, the rejection is not very complex as argued by applicants. If a person of ordinary skill in the art typically engages in such experimentation, the complex nature of a reaction does not provide evidence of non-obviousness. It is common practice for a person of ordinary skill in the art to attempt to modify known reaction mechanisms in order to reduce the number of steps, and Chu-Moyer et al. teaches the necessary reaction conditions to do

so. Applicants have not supplied any objective evidence to support their case for unobviousness. To this end, arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). The rejection is still deemed to be proper and is maintained for at least the foregoing reasons.

### ***Conclusion***

17. No claim is allowed
18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia L. Otton whose telephone number is (571)270-7683. The examiner can normally be reached on Monday - Thursday 8:00-6:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

**THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

/Alicia L. Otton/  
Examiner, Art Unit 1626

/Rebecca L. Anderson/  
Primary Examiner, Art Unit 1626